ESSAYS ON APS CLASSIC PAPERS

The beginning of a fantastic, unanswered question: is 5-HT involved in systemic hypertension?

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This essay examines the historical significance of an APS classic paper that is freely available online:

Serotonin (5-hydroxytryptamine, 5-HT) was one of the first vasoactive amines to be discovered. As 5-HT is concentrated in the blood platelet to near millimolar concentrations, one might suspect that 5-HT would have significant impact as to how blood vessels, which carry the platelet, would function. In 1970, Don D. McGregor and Sir Horace Smirk (Figs. 1 and 2; kindly provided by Dr. Janet Ledingham, New Zealand) of the Otago University Medical School published a paper in the American Journal of Physiology (5) that began a line of research in hypertension investigating questions that are still being argued.

Their paper was entitled “Vascular response to 5-hydroxytryptamine in genetic and renal hypertensive rats” (5). The purpose of this study was to determine whether the mechanical advantage that an artery possessed in hypertension (thicker, stiffer wall compared with normal vessel) could completely explain the hyperreactivity to agonists, such that responses to agonists would be equivalently enhanced. Their experiments were straightforward and telling.

They used two models of hypertension. The first was an inbred strain of New Zealand rats that develop hypertension genetically (GH), and the second was a renal model of hypertension in which a small silver clip was placed on the renal artery of the right kidney (2 kidney, 1 clip). Normal Wistar rats were used as controls. The effects of intravenous 5-HT on arterial blood pressure was examined in the chloralose-anesthetized state. Additionally, mesenteric arterial perfusion pressure in the isolated mesenteric arcade exposed to 5-HT, norepinephrine (NE), or angiotensin II (ANG II) was also measured.

Rats with hypertension had a profound increase in reactivity to 5-HT. A dose of 5-HT that elevated blood pressure of Wistar rats by 47 mmHg increased arterial pressure of the GH rat by nearly twice as much (92 mmHg). When ganglionic transmission was blocked pharmacologically, blood pressure fell in both strains, but the GH continued to be more sensitive and reactive to 5-HT. This suggested that an element independent of the sympathetic nervous system/ganglionic activity was responsible for mediating the elevation in blood pressure; systemic arteries were a likely candidate. Their findings in the isolated perfused mesentery bear this idea out, as 5-HT was more potent and efficacious in the GH compared with Wistar. Similar enhancements to ANG II and NE were only modestly observed. These data provided the important evidence that it was not just the structural change the arteries from the hypertensive animal underwent (thicker media, stiffer wall) that caused hyperreactivity. At the time of this report, 5-HT receptors were not well defined and known only as “D” or “M” receptors (3). McGregor and Smirk (5) demonstrated that the increase in perfusion pressure to 5-HT could be blocked by a 5-HT receptor antagonist, xylamidine tosylate.

Thus began decades of research dedicated toward understanding how 5-HT may play a role in hypertension. A slew of studies using isolated arteries and arterial beds from different models of hypertension support the original finding of McGregor and Smirk (5). The threshold for arterial contraction/pressure increase to 5-HT was lower, potency of 5-HT higher, and the maximal effect 5-HT could cause also higher in the hypertensive rat compared with a normotensive control (for review, see Ref. 10). In 1979, Peroutka and Snyder (7) defined 5-HT1 and 5-HT2 receptors. Presently, 5-HT receptors are
5-HT: good or bad guy? More recently, studies in the human suggest an elevated level of circulating plasma 5-HT in hypertensive vs. normotensive subjects (1); elevations in free plasma 5-HT have also been observed in laboratory models of hypertension (9). Thus, the question still remains: does 5-HT play a role in control of normal vascular tone, and in particular the elevated vascular tone observed in hypertension?

Fig. 2. Sir Horace Smirk.

divided into seven different subtypes (5-HT1 through 5-HT7), and multiple subtypes of some of these receptors also exist. Development of selective serotonergic receptor agonists and antagonists allowed investigation as to which 5-HT receptor subtype was responsible for arterial contraction and whether this changed in hypertension. Investigators discovered that several 5-HT receptors (5-HT1B/1D, 5-HT2A, 5-HT2B, and 5-HT7) are important in the vasculature. 5-HT could cause both contraction and relaxation in vascular beds. Introduction of ketanserin (Janssen Pharmaceuticals) as a 5-HT2A receptor antagonist also stimulated research in 5-HT in hypertension, as ketanserin caused a significant reduction in blood pressure of hypertensive animals (9). However, it was discovered that ketanserin had significant affinity for the α1 adrenergic receptor, and this interaction was thought to be primarily responsible for the fall in blood pressure. This put the field in a state of confusion as to whether 5-HT was causally involved in high blood pressure.

REFERENCES